Management of Diagnosis and Treatment in a Case of Fibrolamellar Carcinoma

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Abstract. Background/Aim: Fibrolamellar carcinoma is a rare primary hepatic malignancy that has recently been recognized as a distinct clinical entity, highly different from the well-known hepatocellular carcinoma. This report describes the clinical and paraclinical aspects of the fibrolamellar carcinoma, emphasizing its particularities. Case Report: A 30-year-old patient presented to the hospital with nonspecific symptoms and weight loss, with imaging findings showing abdominal and mediastinal masses. Multiple biopsies were performed, leading to a diagnosis of metastatic fibrolamellar carcinoma. Given the extent of the disease, systemic drug treatment was administered, although prognosis was poor with tumor growth, resulting in biliary duct invasion. Conclusion: Fibrolamellar carcinoma is a rare type of malignancy, with a difficult differential diagnosis in which imaging techniques are important but for which biopsy remains the gold standard. The prognosis depends on tumor extent and may include surgical methods or chemotherapy.

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Fibrolamellar carcinoma (FLC) is a rare pathological entity that was first described by Edmondson in 1956 as a histological variant of hepatocellular carcinoma (HCC) (1). The term itself was introduced later, in 1980, by Craig et al., who highlighted the clinical and paraclinical features, recognizing FLC as a distinct type of hepatic malignancy (2, 3). Considering its unique clinical, biological and histological characteristics, FLC was recently given its own World Health Organization classification number (4).

Differences between HCC and FLC start with the etiology of the disease, with no established risk factors for FLC. This particular tumor type appears to be more frequent in young patients, discovered either incidentally or with non-specific symptoms. No serological marker has been found specifically linked to FLC and imaging investigations reveal no particularities. Ultimately, the differential diagnosis is based on the histological aspect of the tumor; thus, a positive diagnosis requires either fine-needle aspiration (FNA) biopsy or specimens obtained intraoperatively.

Literature data show that patients diagnosed with FLC can benefit from aggressive surgical treatment, such as liver transplantation or liver resection. Trans-arterial chemo-embolization may also be a useful option in some cases (5).

Case Report

We present the case of a 30-year-old man, with no prior medical history, who was admitted to our hospital with ongoing lumbar pain, important weight loss (approximately 10 kg), nausea and malaise – symptoms that were persistent
over the previous two months. Patient consent was obtained prior to the publication of this article.

Physical examination was normal, with no palpable abdominal mass or hepatomegaly, no palpable peripheral lymphadenopathy and no ascites. The alpha-fetoprotein (AFP) level was highly elevated (451.90 ng/ml), the peripheral blood tests were otherwise within normal limits. The patient had abdominal ultrasonography performed at another facility which had described intrahepatic masses.

For better characterization, computerized tomography of the thoracic, abdominal and pelvic regions was carried out. The exploration revealed an adenopathic tumoral mass, with inter-hepato-gastro-pancreatic development and iodophilic nature, with small necrotic areas within, involving the celiac trunk and its branches and creating a mass effect on the hepatic pedicle. A hepatic tumoral mass of about 55/40 mm was also described within segment IVB.

In the thoracic region, the computed tomography scan revealed the presence of a tumoral lymphadenopathy of about 75×55 mm, located in the right cardio-phrenic angle, with similar characteristics to those of the hepatic mass. Upper endoscopy, colonoscopy and echocardiographic examination were normal.

Given the presence of mediastinal lymphadenopathy, the patient was referred for an endoscopic ultrasound examination, during which a trans-esophageal endoscopic ultrasound-guided FNA was performed. The microscopic analysis showed enlarged cells with eosinophilic cytoplasm and large nuclei with prominent nucleoli, thus leading to the hypothesis of metastatic hepatic malignancy.

The patient was transferred to the General Surgery Clinic, where a laparotomy was performed, revealing a hemorrhagic tumoral mass, with inter-hepato-gastro-pancreatic localization, for which the chosen surgical management on site included partial resection with hemostasis. The lesion was considered not to be completely resectable because of its extensive vascular involvement. Multiple lymphadenopathies were also assessed, as well as the hepatic segment IV mass – most

Figure 1. Computerized tomography (CT) of the abdominal region. A: CT revealed a tumoral inter-hepato-gastro-pancreatic mass, characterized by iodophilic nature, with small necrotic areas; the tumor had invaded the celiac trunk and its branches, creating a mass effect on the hepatic pedicle. B: CT with emphasis on a hepatic tumoral mass, described within segment IVB.

Figure 2. Computerized tomography of the thoracic region, revealing tumoral lymphadenopathy of ~75×55 mm, located in the right cardio-phrenic angle.
probably the primary tumor, as revealed by computed tomography shown in Figures 1 and 2.

Macroscopically, the histopathological examination described an encapsulated grey nodal mass of about 10×6×5.5 cm, with necrotic areas at the section surface. Microscopically, it showed malignant epithelial proliferation, with polygonal-shaped cells, with eosinophilic cytoplasm and voluminous hyperchromatic nuclei, having intranuclear inclusions and atypical mitoses shown in Figure 3A. The aforementioned tumoral proliferation was also characterized by trabecular and alveolar nature, as well as by important intracellular lamellar collagenous fibrosis shown in Figure 3B and C, being compatible with the histopathological diagnosis of FLC.
Immunohistochemical tests were positive in the cytoplasm for cytokeratin 8/18 (CK8/18), CD68 antibody, deletions in glypican 3, CK7 and CK19 (Figure 3D-H, respectively); positive in the blood vessels for CD34, negative for CD10 and weakly positive in the cytoplasm for epidermal growth factor receptor (Figure 4). The immunohistochemical pattern, therefore, confirmed the histopathological diagnosis.

The result of the biopsy was analyzed in the context of the extent of disease by a multidisciplinary team that included an internist, a surgeon and a specialist in medical oncology, who recommended the administration of sorafenib.

After about 2 months of taking sorafenib with good tolerance and apparently good response, the patient presented at the hospital with jaundice, most probably due to tumoral growth and tumoral biliary obstruction. The laboratory findings showed elevated levels of alanine transaminase and aspartate transaminase, at about five times the normal values. Total bilirubin was 13.91 mg/dl, with direct bilirubin of 13 mg/dl. Alkaline phosphatase and gamma-glutamyltranspeptidase were also significantly increased (550 U/l and respectively 905 U/l). The patient also had moderate anemia (with hemoglobin of 8.8 g/dl). An external-internal biliary drainage was performed, thus leading to the reduction of the bilirubin level and the remission of jaundice. Treatment with sorafenib was interrupted, considering the progression of the tumor under therapy, and subsequent episodes of cholangitis after biliary drainage. The patient was lost to follow-up 7 months after diagnosis.

Discussion

In this article, we report the case of a FLC, diagnosed in a young patient with no comorbidities – a pattern that is consistent with the literature description of this type of tumor.

While the development of HCC is based on active hepatic inflammation, viral infection, alcohol-related alterations, non-alcoholic fatty disease, cirrhosis or dietary aflatoxin B1, the mechanisms that lead to FLC remain unclear, as it usually occurs in the absence of liver injuries (such as inflammation or fibrosis), with no histological findings of precursor lesions (6). Although no etiological relationship has been demonstrated, it has been noted that FLC resembles focal nodular hyperplasia with a central scar, both affecting young individuals and sharing several imaging and histological features, such as a stellate central scar in imaging findings, and copper accumulation in histological examinations (7, 8). Genetic mutations involved in the development of FLC may include a deletion on chromosome 19, as a recent study showed (9). Advances in gene sequencing have determined the detection of a recurrent DNAJ heat shock protein family (Hsp40) member B1–protein kinase cAMP-activated catalytic subunit alpha chimeric transcript fusion protein (DNAJB1–PRKACA) to be the driver mutation for FLC, thus opening the way for new targeted therapeutic approaches (10).

FLC typically affects young individuals. The clinical signs and symptoms may include abdominal pain, weight loss, fatigue, malaise (2). However, in some cases, the disease remains clinically silent and the carcinomatous nodule is discovered incidentally. There have also been reported signs of biliary obstruction due to tumoral invasion of the biliary tree, or even due to metastatic compression (3, 11-13). Gynecomastia may also appear in some cases (14). A recent study has shown that the majority of patients complain of abdominal pain, abdominal distension, anorexia, fever and jaundice as main symptoms (15).

Biological markers are equally as non-specific as the clinical presentation. Usual blood biochemistry and cell counts are within normal limits (11). The serum level of AFP is usually within the normal range, although there might be situations of increased blood AFP level associated with FLC. However, there is a high possibility that the few reported cases of FLC with high levels of AFP are in fact misdiagnosed HCCs as the differential diagnosis between the two types of tumors remains a significant problem (6). Some authors have also described a close association between elevated serum vitamin B12 level and the presence of FLC (15, 16).

Imaging studies in FLC mostly describe a large, well-defined tumor, possibly with a central scar or calcification (17). The mass is heterogeneously enhanced and the typical HCC aspect of arterial enhancement with portal wash-out is not visible. Fewer than 10% of cases present with portal vein thrombosis or biliary obstruction. Medical literature reports only a few cases of metastatic FLC, distant metastatic disease being described mostly of the lungs, peritoneum and adrenal glands (15-18). There are even fewer literature cases where
metastases are characterized using FNA, since this method may result in the aspiration of malignant hepatocytes, without fibrotic lamellae (thus leading to a false diagnosis of HCC and not FLC) (18, 19). The most objective and effective means of differentiating between the two types of hepatic masses remains, therefore, the histopathological analysis (20).

Among the particularities of our case, we note the association of a high AFP levels at diagnosis, as FLCS often do not produce AFP (fewer than 10% of the patients diagnosed with FLC have an AFP level higher than 200 ng/ml) (21). Furthermore, we noted that the patient had lymph node metastases, both mediastinal and abdominal, at admission. Although the FNA of the mediastinal lymphadenopathy result was not suggestive of the diagnosis of FLC, it undoubtedly testified to the hepatic origin of the lymph node metastasis. However, a final diagnosis was not possible until an exploratory laparotomy with biopsy was performed, confirming the presence of FLC.

Once diagnosed, the prognosis of FLC remains unclear. It is reported to be associated with a higher survival rate than HCC, as FLC is not associated with chronic liver disease (22). Whenever possible, the main therapeutic approach should be liver resection or transplantation, taking into account the fact that these patients are usually young, without comorbidities (5). Nevertheless, there is a high rate of recurrence as late as 5 years after resection, mainly due to the presence of nodal metastases at the time of the first intervention (12). More than 50% of patients undergoing liver transplantation present disease recurrence (23). This may be due to the fact that current indications for transplantation in patients with FLC include advanced disease. Recent reviews suggest that after surgical resection, FLC has a better prognosis than HCC but survival rates after transplantation do not differ significantly (24, 25). In our patient’s case, despite the absence of cirrhosis, the poor prognosis was suggested by the presence of metastatic disease and, therefore, by the contraindication of aggressive surgical treatment, such as liver transplantation or tumor resection.

It is considered that if the tumor is unresectable, median survival is 14 months (26). Treatment options in this case include systemic therapy or transarterial chemoembolization, until the development of new molecule-targeted drugs. The only approved treatment is sorafenib, as ‘orphan product’, given the lack of statistically supporting evidence or alternative therapy. Small studies on therapy with 5-fluorouracil and recombinant interferon α-2b (27) or platinum salts (28) have shown their higher efficacy in FLC than HCC, however, without statistical significance or major improvement in overall survival. Due to the rarity of this disease, especially when associated with the presence of metastasis, there is not enough data concerning the use and efficacy of sorafenib in patients with metastatic FLC. However, since the drug targets both tumor growth and neoangiogenesis, it can be considered as a choice in treating patients with FLC. In the presented case, the patient had very good tolerability to the chemotherapy agent (one of the reasons being the fact that he had no associated comorbidities) but the disease seemed to be progressive despite its use, leading to tumor growth and biliary duct obstruction, with jaundice.

**Conclusion**

FLC is a peculiar entity at both histological and molecular levels. It affects young individuals, in the absence of liver cirrhosis, therefore leading to a good prognosis when it is limited to hepatic localization. When metastatic, it is associated with a poor outcome. Differential diagnosis is difficult, and, although imaging findings are crucial, biopsy remains the gold diagnostic standard. The use of chemotherapy in metastatic FLC is considered controversial, as there are not enough literature data to support its efficacy.

**Conflicts of Interest**

None declared.

**Author’s Contributions**

BH and RA analyzed and interpreted the patient data and performed critical review of the article. AFZ, XB, AMS and LT analyzed the data and made major contributions in writing the article. MG interpreted the imaging findings of the patient. MD performed the critical review of the literature. AM were involved in the surgical management of the patient and performed the literature review. VH performed the histological examination of the tumor and was a major contributor in writing the article. All Authors read and approved the final article.

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